MINI-SYMPOSIUM: Astroglia in Neurodegenerative Diseases

Stratification of astrocytes in healthy and diseased brain

Alexei Verkhratsky [1,2,3]; Robert Zorec[4,5]; Vladimir Parpura[6]

[1] Division of Neuroscience & Experimental Psychology, The University of Manchester, Manchester, United Kingdom.
[2] Achúcarro Basque Center for Neuroscience, IKERBASQUE, Basque Foundation for Science, 48011 Bilbao, Spain.
[3] Department of Neuroscience, University of the Basque Country UPV/EHU and CIBERNED, 48940 Leioa, Spain.
[4] Laboratory of Cell Engineering, Celica BIOMEDICAL, Tehnološki park 24, Ljubljana 1000 Slovenia, Europe.
[5] Laboratory of Neuroendocrinology-Molecular Cell Physiology, Institute of Pathophysiology, Faculty of Medicine, University of Ljubljana, Zaloška 4, Ljubljana 1000, Slovenia, Europe.
[6] Department of Neurobiology, Civitan International Research Center and Center for Glial Biology in Medicine, Evelyn F. McKnight Brain Institute, Atomic Force Microscopy & Nanotechnology Laboratories, 1719 6th Avenue South, CIRC 429, University of Alabama at Birmingham, Birmingham, AL 35294-0021.

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Corresponding author:
Prof. Alexei Verkhratsky MD, PhD, DSc, Faculty of Life Sciences, The University of Manchester, Manchester, UK
(E-mail: *Alexej.Verkhratsky@manchester.ac.uk*)

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Abstract

Astrocytes, a subtype of glial cells, come in variety of forms and functions. However, overarching role of these cell is in the homeostasis of the brain, be that regulation of ions, neurotransmitters, metabolism or neuronal synaptic networks. Loss of homeostasis represents the underlying cause of all brain disorders. Thus, astrocytes are likely involved in most if not all of the brain pathologies. We tabulate astroglial homeostatic functions along with pathological condition that arise from dysfunction of these glial cells. Classification of astrocytes is presented with the emphasis on evolutionary trails, morphological appearance and numerical preponderance. We note that, even though astrocytes from a variety of mammalian species share some common features, human astrocytes appear to be the largest and most complex of all astrocytes studied thus far. It is then an imperative to develop humanized models to study the role of astrocytes in brain pathologies, which is perhaps most abundantly clear in the case of glioblastoma multiforme.

INTRODUCTION: THE CONCEPT OF HOMEOSTATIC NEUROGLIA

The complexity of human brain is remarkable: more than 200 billions (ie, 2×10^{11}) of neural cells (neurones and neuroglia) are packed within a limited volume (average human brain occupies 1200–1400 cm^3). These neural cells form complex networks, connected with 15–20 trillions of chemical and electrical synapses that provide for this organ computing power. Assuming the memory capacity of a single chemical synapse of ~ 5 bits, the total memory capacity of the human brain exceeds 1 petabyte (21). The logistics support underlying this highly complex analytical machine (which uses multiple information processing algorithms being thus fundamentally different from binary-oriented artificial computing) is provided by a specific class of cells known as neuroglia.

Neuroglia, which comprise cells of neural (astrocytes, oligodendrocytes and NG2 glia and all peripheral glia) and non-neural (microglia) origins, represent the homeostatic and defensive arm of the nervous system (110, 260). Glial cells provide homeostatic control on all levels of organization of the CNS (Table 1) from molecular (eg, regulation of ion and neurotransmitter turnover) to network (eg, regulation, of synaptic connectivity and axonal myelination) and systemic (chemosensing and regulation of energy balance). Astrocytes, which are distributed in both white and gray matters of the brain and the spinal cord, are main homeostatic cells (174, 263); oligodendrocytes are responsible for axonal myelination and axonal homeostatic support throughout the brain, being thus central elements of the brain connectome (73); NG-2 glia contribute to CNS homeostasis, and provide a pool of oligodendroglial progenitor cells involved in adult (re)myelination (158, 208). All these macroglial cells are responsible for CNS protection and defence through a complex and evolutionary conserved programme of reactive astrogliosis, Wallerian degeneration and activation of NG2 glia (178, 203, 260, 266). Microglial cells [which enter the brain as foetal macrophages—(80)] acquire a specific morphological phenotype (small cell bodies with highly motile processes) and express an extended complement of receptors characteristic for both neural and immune cells. Combination of motile processes and multiple receptors are instrumental for constant surveillance of the nervous tissue for the signs of damage (108). Microglial cells shape neuronal networks through synaptic stripping and phagocytosis of redundant and apoptotic neurones during development (109, 252). Insults to the brain trigger microglial activation, which produces multiple and often disease-specific phenotypes, while overactivation of microglia may assume neurotoxic proportion and exacerbate neuropathology (92, 108).

Table 1. Physiological functions of astroglia.

Function	Molecular pathways	Reference
Ion homeostasis		
K^+ buffering and homeostasis	Na^+-K^+ pump, NKA	(41, 51, 115, 122, 132, 164, 171, 172, 192, 225, 254)
	Na^+-K^+-Cl^- co-transporter 1 NKCC1/SLC12A2 (operational at high K^+ loads)	
	Inward rectifier K^+ channels $K_{ir}4.1$	
	Connexins Cx43, Cx30	
Cl^- homeostasis	$GABA_A$ receptors	(24, 65, 107, 173, 230)
	Anion channels, ClC-2,	
	Volume-regulated anion channels VRAC/SWELL1	
	Best1 Cl^- channels	
	Na^+-K^+-Cl^- co-transporter 1 NKCC1/SLC12A2	
H^+ homoeostasis and control of extracellular pH	Na^+-H^+ exchanger NHE1/SLC9A1	(40, 54, 84, 89)
	Na^+-HCO_3^- transporter NBCe1/SLC4A4	
	Plasmalemmal V-type H^+ pump	
Na^+, Ca^{2+} homoeostasis	Plasmalemmal Ca^{2+} pump PMCA	(112, 114, 206, 265, 268)
	Na^+-Ca^{2+} exchanger NCX1/SLC8A1, NCX2/SLC8A2 and NCX3/SLC8A3	
Neurotransmitter homoeostasis		
Glutamate	Na^+-dependent glutamate transporters EAAT1/SLC1A6 and EAAT2/SLC1A2	(113, 257, 293)
	Cystine/glutamate antiporter Sxc^- composed of xCT/SCL7A11 and 4F2hc/SLC3A2 proteins	(6, 151)
GABA	Na^+-dependent GABA transporter GAT3/SLC6A11	(148, 223)
Glutamate/GABA-glutamine shuttle	Glutamine synthetase GS	(96, 163, 205)
	Na^+-dependent glutamine transporters	
Glycine	Na^+-dependent glycine transporters GlyT1/SLC6A9	(69, 100, 288)
Monoamines	Norepinephrine transporter NET/SLC6A2 (which transports both noradrenaline and dopamine)	(221, 247)
	Monoamine oxidase B MAO-B	(95, 212)
Adenosine	Na^+-dependent concentrative nucleoside transporters CNT2/SLC28A2 and CNT3/SLC28A3	(127, 183)
	Adenosine kinase ADK	(27, 242)
Metabolic support		
Uptake of glucose, synthesis of glycogen	Glucose transporter	(5)
Aerobic glycolysis, shuttling of lactate to neurones	Monocarboxylate transporters 1 and 4 (MCT1/SLC16A1, MCT4/SLC16A3	(87, 180, 181)
Network homeostasis and synaptic transmission		
Synaptogenesis	Cholesterol, thrombospondins, hevin, secreted protein acidic and rich in cysteine SPARC	(67, 119, 139, 187)
Synaptic maturation	Activity-dependent neurotrophic factor, tumor necrosis factor α (TNFα), cholesterol, astroglia-derived glypicans 4 and 6	(7, 67, 187)
Synaptic extinction	Complement factor C1q	(42, 214)
Organ homeostasis		
Regulation of the formation and permeability of blood-brain and CSF-brain barriers		(1, 2)
Formation of glial-vascular interface and regulation of microcirculation	Epoxyeicosatrienoic acids EETs,	(18, 74, 101, 144, 153, 246, 294)
	20-hydroxyeicosatetraenoic acid 20-HETE, prostaglandin E_2 PGE_2,	
	Ca^{2+}-dependent K channels $K_{Ca}3.1$	
Functional operation of the glymphatic system	Water channel aquaporin-4 AQP4	(102, 103, 154, 156)
Gliocrine system, astrocytes act as secretory cells of the brain	Neurotransmitters, neuromodulators, neurohormones, cytokines, neurotrophic factors	(259, 262, 296)
Systemic homeostasis		
Central chemoception of plasma Na^+ concentration	Na^+-activated Na_x channels	(159, 160, 229, 277)

Table 1. *Continued.*

Function	Molecular pathways	Reference
Central chemoreception of oxygen, pH and CO^2	Oxygen sensor associated with mitochondria in cortical astrocytes pH sensor in brain stem astrocytes Na^+-Ca^{2+} exchanger. $K_{ir}4.1$ K^+ channels	(12, 83, 253, 279)
Regulation of sleep	Astrocytes are linked to the sleep homeostat through an elevation of brain adenosine content in the wake state. Astrocytes may also regulate sleep through dynamic control over ion composition of the interstitium	(60, 86, 188, 248)

EVOLUTION OF GLIA ACCOMPANIES INCREASING COMPLEXITY OF THE BRAIN

Evolutionary emergence of the supportive neural cells coincided with the centralization of the nervous system and appearance of neuronal conglomerates in the form of ganglia or neuronal rings. The ancient forms of neuroglia, defined as cells covering neuronal elements have been characterized in round worms and in the Acoela worms. The nervous system of the round worm *C. elegans* comprises 302 neurones and 50 supportive cells of the ectodermal origin (which can be classified as neuroglia) and six GLR cells originating from mesoderm, these later being interconnected (through gap junctions) to both neurones and muscle cells (168). The majority (46) of glial cell of *C. elegans* are forming (together with neuronal terminals) the sensory organs of the worm, known as sensilla. Four ensheathing glial cells localized in the head of the *C. elegans* extend velate processes covering neurones in the neural ring of the animal, and thus can be defined as proto-astrocytes (185, 240). The supportive cells extending multiple processes into the neuropil were also identified in the Acoela worms (25); in platyhelminthes (polyclads and triclads) supportive cells have been found in the nerve cord (82).

Further evolution brought up a substantial diversification of glia. The ganglionic nervous system of the medicinal leech contains several types of specialized glia, represented by giant glial cells responsible for homeostatic control over the neuropil, by packet glial cells which enwrap neuronal cell bodies and by connective glial cells that cover and support axons (55). The giant glial cells express multiple ionotropic and metabotropic neurotransmitter receptors and ion channels (55, 152). Neuronal activity and behavioral patterns trigger glial depolarization and cytosolic Ca^{2+} signaling (58, 130). Packet glia regulate K^+ homeostasis around neuronal somata (211), whereas giant glial cells control ion homeostasis in the neuropil, being particularly important for regulation of pH (by plasmalemmal Na^+-HCO_3^- co-transporter, Na^+-H^+ and Cl^--HCO_3^- exchangers). Furthermore giant glial cells remove extracellular glutamate and choline through dedicated Na^+-dependent plasmalemmal transporters (56, 57, 98, 283).

Even higher level of diversification characterizes neuroglia in the arthropods, and particularly in the insects. In *Drosophila,* glial cells account for ~10% of all cells in the CNS and are represented by several major classes. These include: (i) wrapping glia of the peripheral nervous system; (ii) surface glia (comprising perineural and subperineural cells), which make the brain-hemolymph barrier; (iii) cortex glia that cover neuronal cells bodies in the CNS; (iv) neuropil glia (ensheathing and astrocyte-like glia) that cover CNS axons and synapses; and (v) tract glial cells, which cover axonal tracts connecting different neuropils in the CNS (8, 64, 76, 90, 117). The major types of glial cells are further subdivided on a basis of their morphology and function; for example, the glia of the lamina (neuropil) of the optic lobe is classified into fenestrated glia, pseudocartridge glia, distal and proximal satellite glia, epithelial glia and marginal glia (38, 64, 250). Glial cells in insects are responsible for homeostatic functions, such as regulation of ionic balance in the CNS fluids and regulating clearance, recycling and metabolism of neurotransmitters (29, 140). In particular neuropil glial cells in *Drosophila* express glutamate receptors (133), excitatory amino acid transporters dEAAT1and dEAAT2, as well as glutamine synthetase generating glutamine the glutamate-glutamine cycle, the latter responsible for transport and recycling of glutamate between neurones and glia (53, 106).

In early vertebrates, the CNS parenchymal glia is replaced by the radial glia, which is associated with an emergence of layer organization of the brain. In the early chordates and in the low vertebrates (eg, in sea cucumber, star fishes, chondrichthian fishes and teleosts) the radial glia is the only type of parenchymal glia responsible for both neurogenesis and homeostatic control over the nervous tissue (16, 32, 136, 137). Increase in the thickness of the brain is accompanied with the emergence of the parenchymal astrocytes, which cover an increased homeostatic demand associated with the brain size (196, 280). In higher vertebrates radial glia generally disappears after birth, with some types of radial astroglial remaining in the cerebellum (Bergmann glia), in the retina (Müller glia) and in the hypothalamus (tanycytes).

ASTROGLIA: DEFINITION AND APPEARANCE

The name of astrocyte was invented by Michael (Mihály) von Lenhossék (125) to define a subclass of parenchymal glia; Lenhossék also proposed to call all neuroglial cells of the gray matter spongiocytes. Astroglia are defined as a highly heterogeneous class of neural cells of ectodermal, neuroepithelial origin that sustain homeostasis and provides for defence of the central nervous system (260). Astroglia are further sub-classified into protoplasmic astrocytes of the gray matter, fibrous astrocytes of the white matter, velate astrocytes of the cerebellum, radial astrocytes (represented by Müller retinal glial cells, cerebellar Bergmann glial cells and

tanycytes of the hypothalamus and parts of the spinal cord), pituicytes in the neuro-hypophysis, perivascular and marginal astrocytes, Gomori-positive astrocytes (rich in iron and identified in the arcuate nucleus of the hypothalamus and in the hippocampus) and surface-associated astrocytes. In addition, astroglia include several types of cells that line the ventricles or the subretinal space represented by ependymocytes, choroid plexus cells and retinal pigment epithelial cells The brains of the high primates contain specific interlaminar, polarized and varicose projection astrocytes (260).

Identification and visualization of astrocytes in the nervous tissue relies on the morphological criteria and expression of specific markers. The latter include glial fibrillary acidic protein (GFAP), vimentin, protein S100, plasmalemmal glutamate transporters EAAT-1 and EAAT-2 (known in rodents as GLAST and GLT-1, respectively), glutamate synthetase, inward rectifying $K_{ir}4.1$ channels, water channels aquaporin 4 (AQP4), connexins Cx30 and Cx43, aldehyde dehydrogenase 1 family member L1 (ALDH1L1) foliate metabolism enzyme, fructose-1, 6-bisphosphate aldolase (or aldolase C), and transcription factor SOX9 (13, 14, 35, 36, 154, 161, 167, 176, 213, 218, 244, 275). None of these markers, however, labels all astrocytes throughout the brain.

The most commonly used immunostaining with antibodies against GFAP visualizes only a sub-population of astrocytes with a substantial regional and developmental heterogeneity. In the juvenile hippocampus anti-GFAP staining reveals ~ 80% of all astroglia (35, 167), whereas in other regions of the healthy brain only a minority (10–20%) of astrocytes are GFAP-positive (111, 213, 276). In addition GFAP staining reveals only the main processes of astrocytes, with no labeling of perisynaptic and peripheral processes or small endfeet, thus labeling only ~15% of an individual astrocyte (195, 231). Immunostaining with antibodies against protein S100B labels, as a rule, 2–3 times more astroglial compartments compared with GFAP labeling (167, 213). At the same time immunoreactivity for S100B is detected in other CNS cells including oligodendrocytes, ependymal cells, choroid plexus epithelium, vascular endothelial cells, and even in some neurones (199, 237). The antibodies against EAAT-1 (the most widespread astroglial glutamate transporter) stain radial glia, fibrous and protoplasmic astrocytes, cerebellar Bergmann glia, retinal Müller glia, radial stem glia in the dentate gyrus and subventricular zone in developing and adult CNS (20, 228, 281). Some splice variants of EAAT-1, however, were found in some neurones, oligodendrocytes and ependymal cells (217). Of note, EAATs expression show substantial inter-species differences (281). Immunoreactivity for glutamine synthetase (GS) was detected in fibrous and protoplasmic astrocytes, in radial glia, Bergmann glia, retinal Müller glia, tanycytes and ependymal cells; furthermore this staining labels many GFAP-negative astrocytes. For example, in the mouse entorhinal cortex, 78% of all labeled glial cells were GS-positive, 12% GFAP-positive and only 10% were positive for both GS and GFAP (286). Similarly, in the hippocampus double staining showed that only 60% of cells immunoreactive for GS were positive for GFAP (276). In addition, staining with antibodies against GS, which is present in the astrocyte cytoplasm, visualizes the complete cellular profile.

Immunolabeling with the water channel AQP4 antibody reveals mainly astroglial endfeet where these channels are concentrated (154), although in human astrocytes this polarization many not be as strict as in mice (66, 189). Antibodies against connexin Cx30 selectively visualize gray matter astrocytes (155), whereas staining against Cx43 does not discriminate between fibrous and protoplasmic astroglia. Polyclonal antibodies against ALDH1L1 stain both GFAP positive and GFAP negative astroglial cells in the cortex; at the cellular level ALDH1L1 - staining allows visualization of fine processes (36). ALDH1L1 is, however, developmentally regulated and it is also expressed in some oligodendrocytes (285). Astrocytes in mouse and human brain are enriched with SOX9, a transcription factor. Immunostaining with specific antibodies against SOX9 exclusively stain astroglial nuclei, and hence are used for *fluorescence activated cell sorting* of astrocytes and for isotopic fractionation (244). Distal and perisynaptic astroglial processes can also be labeled with antibodies against MLC1 protein (28).

For labeling astroglia in the *in vivo* brain, the gliophilic fluorescent probe sulforhodamine 101 and its analogues sulphorhodamine B or G are frequently used (157). This positively charged molecule is selectively taken up by astrocytes and could be delivered either by injection into the brain tissue (157) or even by intravenous injection (15). There is some regional selectivity in rhodamine probes accumulation; it is readily taken up by hippocampal astroglial but does not stain astrocytes in the ventrolateral medulla (220). Rhodamine deployment, however, has some adverse effects on neuronal excitability; rhodamine injections induce seizures *in situ* and *in vivo* (105, 193).

ASTROGLIA: THE NUMBERS

There is still a degree of confusion about the total numbers of neurones and glia, and numerical distributions of different glial cell types in the CNS of mammals. The glia to neurones ratio (GNR) varies considerably between species. The nervous system of invertebrates contains relatively few neuroglial cells, with the GNR in leech, for example, being ~ 0.025; and in *Drosophila* ~0.1. At the same time the buccal ganglia of the great ramshorn snail *Planorbis corneus* contains 298 neurones and 391 glial cells [GNR ~ 1.3 (184)].

In vertebrates the GNR roughly increases proportionally to an increase in the size of the brain; for example, in the cortex the glia to neurone ratio is about 0.3–0.4 in rodents and rabbit, ~ 1.1 in cat; ~1.2 in horse, 0.5–1.0 in rhesus monkey, 2.2 in Göttingen minipig, ~1.5–1.7 in humans, and as high as 4–8 in elephants and the fin whale. Technique of isotopic fractionation developed in recent decade shows that total numbers of neurones and glia in the human brain are similar, although with substantial variations between different brain regions (19, 93). The ratio between non-neuronal cells and neurones varied between 11:1 for the brain stem, 3.7:1 in cortical regions including the corpus callosum and 0.2:1 in the cerebellum (19, 93, 126, 274). The glia to neurone ratio (excluding microglia) in the gray matter of the human cortex was estimated at 1.65 (227). The total number of astrocytes in rodents does not exceed 10–20% of total cells in the brain (244). Based on morphological criteria, in the human neocortex astrocytes accounted for ~ 20%–40%, oligodendrocytes for 50%–75% and microglia for 5%–10% of the total glial population (26, 182). Stereological studies on the cortex of the rhesus monkey, however, demonstrated both developmental and regional differences in numerical distribution of glial cells. In area 17 of young monkeys, for example, astrocytes accounted for 40% of total glia, oligodendrocytes for 53% and

microglia for ~7%. In cortical layers 1–3 astrocytes were at 57%, oligodendrocytes at 36% and microglia at 7%, whereas in the layer 4 (which has higher degree of myelination) 30% of glia belong to astrocytes, 62% to oligodendroglia and remaining 8% for microglia (186).

IDIOSYNCRATIC HUMAN ASTROGLIA

Astrocytes in humans and higher primates differ very much from other mammals (studied so far) in their size and morphological complexity; furthermore, several types of astroglia exist only in the brains of hominids. The protoplasmic astrocytes in the human gray matter occupy ~ 16 times more volume and have ~ 10 times more primary processes compared to the same cells in the rat brain (166). It has been estimated that on average human protoplasmic astrocytes contact and integrate around 2 million of synapses residing in their territorial domains, whereas rodent astrocytes cover ~20 000–120 000 synaptic contacts (35, 166). Human fibrous astrocytes are similarly much larger than rodent ones [the average area of human fibrous astrocyte domain is 180 μm^2 vs. 85 μm^2 in mouse (166)].

The brains of higher primates (old world monkeys and apes) and humans contain several specific types of astrocytes. One of the most abundant types of these cells is represented by interlaminar astrocytes [named so by Jorge Colombo (46)]. These cells were originally described at the end of the 19th century (11, 134, 198). In the human brain, interlaminar astrocytes are characterized by a small (~10 μm) spheroid cell body localized in the cortical layer I; these cells have several short and one or two very long (up to 1 mm) processes, which penetrate through the thickness of the cortex to end in the layers II to IV; terminal portions of these processes appear as bouton- or club-like structures known as terminal masses or end bulbs (43, 166). Incidentally *in vivo* injections of high KCl concentrations increased the number of these terminal masses suggesting association with K^+ homeostasis (44). Often the processes of interlaminar astrocytes contact blood vessels (236). Interlaminar astrocytes appear in first postnatal months and they originate from astroglial precursors and not from radial glia (45). Interlaminar astroglia in the human tissues were reported to be labeled with antibodies against CD44, a receptor for extracellular matrix molecules (3, 236). In addition interlaminar astrocytes show high immunoreactivity for GFAP and S100B, whereas expression of plasmalemmal glutamate transporters and glutamine synthetase seem to be rather low (236). Electrophysiological examination of these astrocytes revealed passive K^+ conductance similar to other types of astroglia; only half of interlaminar astrocytes, however, showed coupling with other astroglial cells (236). Processes of interlaminar astrocytes have been found to be disrupted in Down syndrome and in Alzheimer's disease; furthermore, the size of terminal masses was found to be significantly increased in the latter (43).

Another type of astroglia specific for the brains of high primates and humans is represented by polarized astrocytes. Somata of these cells are located in the deep cortical layers close to the white matter; polarized astrocytes have two exceptionally long (up to 1 mm in length) processes that penetrate into superficial cortical layers (166)

The deep cortical layers also contain a population of cells displaying general properties of protoplasmic astrocytes, but having also several (1–5) very long (up to 1 mm) unbranched processes with evenly spaced varicosities; these processes extend in all directions through the cortex, with many of them contacting blood vessels (166, 236). These cells were identified as "stellate independent cells" by Cajal (37), as varicose projection astrocytes by Oberheim *et al* (166) and as astrocytes with long processes by Sosunov *et al* (236). Similarly to interlaminar astrocytes, these cells can be labeled with antibodies against CD44 (236). The number of these atypical astrocytes with long processes varied very substantially between individual specimens, and they were never observed in neonatal brains, arguably reflecting individual life-long adaptive changes (236).

HUMAN ASTROCYTES AND COGNITIVE CAPACITY—IS THERE A DIRECT LINK?

Highly idiosyncratic properties of human astrocytes (absent in a less intellectually developed mammals) suggest their possible role in information processing and intelligence. Astrocytes can be considered as integrators of neural networks, which may simultaneously influence millions of synaptic contacts. Direct implantation of human foetal glial progenitors into the brains of young immunosuppressed mice resulted in expansion of human cells which eventually populated large portion of the mouse brain largely replacing the host astrocytes (88). Further experiments demonstrated that embryonic human glial progenitors, or glial precursors derived from induced stem cells exhibit a growth advantage and replace the host glia after grafting (81, 282). Animals carrying human astrocytes had improved memory and outperform the wild type animals in several cognitive tests including novel object recognition or auditory fear conditioning (88). Electrophysiological investigations also found a reduced threshold for generation of long-term potentiation in mice living with human astroglia (88). The mechanisms for increased cognitive performance, however, remain unknown; they may reflect higher homeostatic capacity of human astrocytes, different coverage of synapses by astrocytic processes (295) or else increased plasticity stimulated by the release of various factors from human glia.

HUMAN GLIOMA GROWN IN MICE

There are ~ 25 000 new glioma cases recorded annually in the United States (http://www.abta.org/). The most aggressive glioma type is glioblastoma multiforme (GBM; WHO grade IV). The main obstacle to the successful treatment of GBM is its reappearance following surgical removal/radiation therapy in the near vicinity (1–2 cm) of the original locus or, less commonly, by the formation of satellite loci in distant parts of the brain. Both events indicate the invasive nature of this neoplasm (200, 289). Since 1928, it has been recognized that glioma cells have spread throughout the brain by the time patients are symptomatic (52). Yet, GBM extracranial metastases are very rare (0.44%) (200) and multifocal gliomas represent only 0.5%–20% of clinical cases (175). It is the infiltration of GBM cells from a single solid tumor mass into adjacent brain tissue that fits the most common (80%–99.5%) clinical presentation of GBM (216). This migration/invasion needs to be studied as it may represent a fertile ground for novel therapeutic approaches. The most relevant model one can use to study gliomas has been introduced as human patient-derived xenoline (PDX) tumors (78). Here, patient biopsy samples of GBMs are propagated in the brains

Table 2. Astrocytopathology.

Nosological forms	Astrocytopathy	References
Leucodystrophies		
Alexander disease	Sporadic mutations of glial fibrillary acidic protein (GFAP) with pathological remodeling of astrocytes and severe white matter lesions. Decrease in astroglial glutamate uptake	(30, 143, 271)
Megalencephalic leukoencephalopathy with subcortical cysts (MLC)	The disease is caused by mutations in the MLC1 gene often in combination with mutations in the hepatic and glial cell adhesion molecule gene (Hepacam/Glialcam). The MLC1 protein is predominantly expressed in astrocytic end-feet. MLC1 is a part of membrane signaling complex which includes Na^+-K^+- pump, inward rectifier $K_{ir}4.1$ channels, aquaporin4 (AQP4), caveolin-1 and TRPV4 channels. The mechanism possibly involves a loss of astroglial control over fluid homoeostasis and cell volume.	(28, 63, 120, 121, 124, 131)
Vanishing white matter syndrome (VWM) or childhood ataxia with central nervous system hypomyelination (CACH)	Mutations in the eukaryotic translation initiation factor 2 (EIF-2B) gene. The disease is associated with atrophic (dysmorphic) astrocytes, altered GFAP filaments, deficient astroglial reactivity and impaired astrocytic differentiation. Pathologically remodeled astrocytes secret factors inhibiting oligodendroglial maturation.	(31, 59, 61, 256)
Demyelinating diseases		
Neuromyelitis Optica (NMO)	Autoantibodies-induced loss of AQP4 and GFAP, astroglial atrophy and demise.	(97, 194)
Baló's disease	Down-regulation of expression of Cx43 and AQP4, mislocalization of MLC1, astroglial hypertrophy. Loss of astroglial function is considered to be a primary cause for oligodendroglial lesions and demyelination.	(135, 138)
Neurotoxic encephalopathies		
Hepatic encephalopathy	Pathological remodeling of astrocytes; failure of K^+ and glutamate homeostasis with ensuing excitotoxicity, pathological Ca^{2+} signaling and aberrant glutamate release, deficient operation of glutamate-glutamine shuttle because of excessive ammonium obliterating the GS pathway.	(4, 85, 150, 162, 165)
Heavy metal (lead, manganese mercury, aluminum)-induced encephalopathies	Astroglial loss of function: accumulation of heavy metal into astrocytes instigated significant down regulation of plasmalemmal glutamate transporters with ensuing excitotoxicity.	(241, 243, 269, 287)
Wilson disease	Pathological remodeling of astrocytes; failure of astroglial regulation of copper homoeostasis.	(62, 215, 249)
Psychiatric diseases		
Wernicke-Korsakoff encephalopathy	Loss of astroglial function: substantial (up to 80%) down-regulation of astroglial plasmalemmal glutamate transporters with ensuing glutamate excitotoxicity.	(91)
Major depressive disorder	Reduction in astroglial densities in cortex and amygdala, reduced expression of GFAP, decrease in expression of plasmalemmal glutamate transporters, connexins Cx43 and Cx30, glutamine synthetase and AQP4. Impaired astroglial homeostatic capabilities may underlie aberrant neurotransmission responsible for depressive symptoms.	(47–50, 191, 209, 210)
Schizophrenia	Astrodegeneration and astroglial atrophy, down-regulation of homeostatic molecular pathways, including plasmalemmal glutamate transporters, AQP4, GS, thrombospondins. Up-regulation of plasmalemmal cystine-glutamate exchanger and increased production of kynurenic acid may further deregulate glutamatergic transmission and underlie psychotic symptoms.	(71, 190, 219, 222, 270)

Table 2. *Continued.*

Nosological forms	Astrocytopathy	References
Addictive disorders	Combination of astrodegeneration and astroglial reactivity, impaired astroglial glutamate homoeostasis. Ablation of astrocytes from the prelimbic area of the prefrontal cortex, as well as inhibition of astroglial gap junctions increased alcohol seeking behavior. Atrophic astrocytes were observed in nucleus accumbens of cocaine-addicted rats.	(17, 145–147, 197, 224, 278)
Neurodegenerative diseases		
Alzheimer's disease	Astroglial atrophy at the early stages, reactive remodeling of senile plaque associated astrocytes, reduced astrogliosis at the terminal stages, decreased astroglial synaptic coverage, loss of astroglial homeostatic support, impairment of water transport, glutamate uptake and glutamate-glutamine shuttle. Astrocytes associated with senile plaques display Ca^{2+} hyperexcitability and generate abnormal propagating intercellular Ca^{2+} waves.	(104, 118, 129, 170, 201, 202, 204, 261, 264, 267, 273)
Ageing-related tau astrogliopathy	Exclusive expression of pathological tau in astrocytes is the sole histological symptom of several age-dependent dementias.	(116)
Amyotrophic lateral sclerosis (ALS)	Early astrodegeneration, astroglial death (through apoptosis) and loss glutamate clearance function underlie subsequent excitotoxicity and neuronal demise. Selective silencing of human SOD1 mutated gene in astrocytes delays ALS progression. Neuronal death, occurring at later stages of ALS triggers astrogliotic response.	(207, 255, 284)
Parkinson's disease	Astrocytes provide protection of dopaminergic neurones; and astrocytes reportedly may accumulate α-synuclein. There are some evidence for suppressed astroglial reactivity, which may indicate decrease in neuroprotection.	(75, 141, 142, 235)
Huntington's disease (HD)	Progressive astroglial reactivity, although no signs of astrogliosis in HD mouse model. Decrease in glutamate uptake, deficient K^+ buffering, pathologically increased release of glutamate.	(68, 70, 99, 123, 251)
Other diseases		
Glioblastoma	Cancer developed from astrocytes or their precursor's	(149)
Traumatic brain injury	Reactive astrogliosis prevails with a gradient of phenotypes from the lesion to the healthy tissue. Astrocytes move toward the lesion site (anisomorphic astrogliosis) and form the scar. Reactive astrocytes control post-lesion regeneration.	(9, 33, 232)
Ischemia and stroke	Reactive astrocytes surround the area of the infarction core and define survival or demise of neurones in the penumbra. Astrocytes may also convey death signals.	(9, 245, 292)
Epilepsy	Reactive astrogliosis and pathological remodeling of astroglia. Down-regulation of expression of $K_{ir}4.1$ channels, changes in astroglial morphology and disappearance of gap junction coupling were found in astrocytes from hippocampal specimens obtained from patients with mesial temporal lobe epilepsy.	(22, 23, 226, 238)
Migraine	Loss of function mutation of astroglia-specific α2 subunit of Na^+-K^+ pump. Decrease of expression of astroglial plasmalemmal glutamate transporters.	(39)
Autistic spectrum disorders (ASD)	Pathological remodeling of astrocytes is observed in different forms of ASD.	(291)

of immunocompromised mice. These tumors have been genomically, transcriptomically and kinomically profiled, extensively characterized and found virtually identical to human gliomas growing in patients' brains, unlike mouse gliomas that are significantly different (78).

CLASSIFICATION AND COMPLEXITY OF ASTROGLIOPATHIES

The neurono-centric paradigm of neuropathology has been challenged recently; the leading role for neuroglia in shaping the evolution and outcome of neurological disorders begins to be appreciated (34, 79, 174, 178, 233, 271, 272, 291). The modifications of astroglia in neuropathology are multifaceted, often disease-specific and may undergo metamorphoses during the course of pathological evolution (Table 2). Astroglial pathological changes are broadly classified into: (i) astrodegeneration with astroglial atrophy and loss of function; (ii) pathological remodeling of astrocytes and (iii) reactive astrogliosis (178, 261, 266). The first two groups of non-reactive pathological transformation of astrocytes can be summarily identified as astrocytopathies to distinguish from reactive astrogliosis (72).

Astrodegeneration manifests by morphological atrophy, a decrease in astroglial density (through increased cell death) and/or a loss of function; it occurs in many types of neurological disorders. In psychiatric diseases, such as schizophrenia, major depressive disorder or Wernicke-Korsakoff encephalopathy, the number of astrocytes is reduced, and their homeostatic pathways, such as, for example, those associated with glutamate homeostasis, are suppressed (48, 49, 146, 190, 191, 209, 270). These homeostatic failures instigate aberrant neurotransmission or excitotoxic cell death that underlies psychotic symptoms. Morphological atrophy of astrocytes and down-regulation of glutamate uptake are observed in the nucleus accumbens of cocaine-addicted rats (224). Astrodegeneration and astroglial death are contributing to early stages of neurodegenerative diseases such as amyotrophic lateral sclerosis or Alzheimer's disease; in the former, the impairment of astroglial glutamate uptake causes excitotoxic death of motor neurones (207, 255), whereas in the latter, reduced astroglial coverage may explain early synaptic deficiency and early cognitive failures (261, 264, 273). Astroglial atrophy in Alzheimer's disease may also involve changes in secretory vesicles trafficking (239).

Pathological remodeling represents acquisition of abnormal properties by astroglia which drive pathology. This remodeling is evident in several types of leukodystrophies, such as Alexander disease, megalencephalic leukoencephalopathy with subcortical cysts or vanishing white matter syndrome, in which astrocytopathy results in lesions to the white matter (120). In particular, in Alexander disease astroglial expression of mutant GFAP leads to severe leukomalacia (143). Another example of pathological remodeling in astroglia is evident in mesial temporal lobe epilepsy, where astrocytes change their morphology, substantially reduce intercellular coupling and down-regulate expression of $K_{ir}4.1$ channels; these changes lead to a failure in K^+ homeostasis which relates to seizure initiation (22). Pathological remodeling of astroglial function is also observed in specific forms of schizophrenia associated with *Toxoplasma gondii* infection. The parasite targets predominantly astroglia, which causes the aberrant increase in production and secretion of kynurenic acid; this latter being an endogenous inhibitor of NMDA and acetylcholine receptors causes imbalanced neurotransmission to underlie psychotic developments (222).

Reactive astrogliosis is triggered in many neurological disorders. Morphologically reactive astrogliosis is characterized by up-regulation of intermediate filaments such as GFAP and vimentin associated with astroglial hypertrophy (177). Reactive astrogliosis is an evolutionary conserved defensive reprogramming of astroglia aimed at: (i) increased neuroprotection and trophic support of nervous tissue; (ii) isolation of the lesioned area; (iii) reconstruction of the damaged blood-brain barrier; and (iv) providing for post-lesion regeneration of brain circuits (10, 177, 178, 232). Activation of astrocytes is a complex process which arguably produces multiple "reactive" phenotypes, which can be distinct in different diseases. Gene expression profiling of reactive astrocytes demonstrated significant context-dependent (ischemia vs. endotoxin activation) differences (290). All in all, initiation of astrogliotic programme proceeds through a controlled continuum of changes in cellular biochemistry and function that are tuned to the nature and strength of the insult. It seems also that astrocytes within the same lesioned area are heterogeneous in their expression of transcription factors, inflammatory agents and signaling molecules (77, 94). Distinct responses of astrocytes may be due to different densities of receptors, such as β-adrenergic receptors, which, when activated, reduce cytotoxic oedema by inducing astrocytic shrinkage (258).

Conceptually, reactive astrogliosis is a survivalist programme that increases the resilience of the nervous tissue to the environmental insults, while experimental inhibition of astroglial reactivity often exacerbates neuropathology (178). For example, suppression of astroglial reactivity increased both the size of the traumatic lesions and neurological deficit (169). Genetic ablation of GFAP and vimentin reduced astrogliotic response which augmented post-traumatic synaptic loss (176) and resulted in larger ischemic infarcts (128). In the context of neurodegeneration, inhibition of astroglial reactivity increased the β-amyloid load in the animal model of the Alzheimer's disease (179). At the same time, excessive or chronic activation of astrocytes may be maladaptive and may increase the damage of the nervous tissue (177). Astroglial reactivity dominates in acute neurological conditions, such as neurotrauma, ischemic or hemorrhagic stroke or CNS infection. The severity of the insult defines the degree of astrogliotic response, which often results in the formation of glial scar (33, 178, 234). In neurodegeneration astroglial reactivity arises following the appearance of specific lesions, such as senile plaques or Lewy bodies, or is triggered by neuronal death, as, for example, occurs in amyotrophic lateral sclerosis or in Huntington disease (178).

CONCLUDING REMARKS

Astroglia are the homoeostatic arm of the CNS, which make possible the functional activity of nervous tissue. Astrocytes of humans and higher primates differ fundamentally from the same cells in other mammals in their complexity, size and specific subtypes. These differences arguably reflect on an increased complexity of neuronal networks which require extensive support. Grafting of human astrocytes into rodent brains increase (by yet unknown mechanism) the functional performance of the brain. Astrocytes

contribute to all neurological diseases. Astroglial pathological responses are complex and may occur either as a primary pathogenic events which instigate the neuropathology (such as Alexander disease) or secondary responses, which nonetheless contribute to evolution of neuropathology (such as astroglial reactivity in neurotrauma or ischemia). Astroglial pathological changes are multifaceted and can range from degeneration and atrophy to reactivity and pathological remodeling. These different forms of astrogliopathology may occur simultaneously or sequentially following different stages of neuropathology. Regrettably, studies of neurological diseases performed on animal models, most likely do not reveal pathology of human astroglia, and hence urgent need exists in developing "humanized" experimental preparations that may recapitulate astrogliopathy of the human brain.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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